REMARKS/ARGUMENTS

Claims 1, 3-5 and 7-23 are currently pending in the application. Claims 1, 3-5, 7-10, 12-16, and 19, have been amended. Claims 1 and 19 have been amended to indicate that more than one cycle of therapy is administered. Claim 1 has further been amended to indicate that one or more cancer therapeutic also is administered (incorporating Claim 6 into Claim 1). Claims 7-10 and 12-16 have been amended to change the dependency from canceled Claim 6. Claims 3 and 5 were amended to correct minor typographical errors. Claims 2 and 24-28 were previously canceled. Claims 6 and 29-33 are currently canceled.

Claim rejections under 35 U.S.C. §102(b) or §103

The Examiner has maintained the rejection of claims 29-33 under 103(a) as being unpatentable over Webb et al. (The Lancet, 1997 vol. 349:1137-1141) in view of Bennett et al. (U.S. Patent 6,214,986). Applicants have canceled these claims, thus rendering this ground of rejection moot.

Claim rejections under 35 U.S.C. §112

Applicants respectfully submit that the present claim amendments render this ground of rejection moot and accordingly request withdrawal of this ground of rejection.

Claim rejections under 35 U.S.C. 103

The Examiner has rejected claims 1, 3-5, and 13-18 under 35 U.S.C. 103(a) as being unpatentable over Webb et al. (The Lancet, 1997 vol. 349:1137-1141) in view of Waters et al. (Journal of Clinical Oncology, 2000 Vol. 18:1812-1823).

The Examiner notes that Webb does not teach each cycle of therapy separated by an interval of time wherein the human receives no bcl-2 antisense oligonucleotide, and further does not teach or suggest the claimed composition to be used in the recited treatment of regimen. However, the Examiner has argued that it would have been obvious to take the teachings of Webb and Waters and arrive at the present invention.

Applicants disagree and respectfully assert that the Examiner has impermissibly used hindsight to arrive at the claimed invention. Applicants have obtained a Declaration from Dr. Steven Craig Novick, which is attached hereto. In this Declaration, Dr. Novick points out that in his opinion the reference only teaches a two-week treatment regimen. See Declaration, paragraph 10. Dr. Novick also points

out that there is nothing in Webb that would teach or suggest to one skilled in the art to treat a patient for cancer by shortening the regimen to less than the two-week course of treatment, let alone shortening the course of treatment to a cycle of therapy consisting of three to nine days (as is presently claimed in the '170 application). See Declaration, paragraph 11. According to Dr. Novick, one skilled in the art would not be motivated to shorten the course of therapy to treat cancer just because one patient showed reduced bcl-2 levels at week 1 and week 2, especially since patient 6 only showed a partial or negligible tumor response (page 2, column 1139). See Declaration, paragraphs 12-14. Dr. Novick concludes that Webb does not teach or suggest changing the treatment regimen to anything shorter than a two-week course of therapy, let alone to a three to nine day course of therapy as presently claimed in the '170 application. See Declaration, paragraph 15.

Regarding the Waters reference, Dr. Novick concludes that it too only teaches a course of therapy for two weeks. See Declaration, paragraph 16. Dr. Novick also states that just because toxic events in certain patients caused the treatment with bcl-2 antisense oligonucleotide to be discontinued there is no teaching or suggestion to use a shorter course of therapy to treat cancer. See Declaration, paragraph 17.

Dr. Novick also notes that just because Waters reports that certain patients had adverse effects and had their course of therapy terminated, this is no way teaches or suggests using a shorter course of therapy. For example, Patient 15's treatment was discontinued on day one, Patient 16's treatment was discontinued on day 12 and Patient 17's treatment was discontinued after day 2 (48 hours). Dr. Novick points out that, even if one skilled in the art would be motivated to shorten the cycle of therapy to treat cancer, there is nothing in these data to teach or suggest shortening the cycle of therapy to three to nine days, separated by an interval of time when the therapy is not given and repeating with another three to nine day cycle of therapy (as the current pending claims require). See Declaration, paragraph 18. Concurring with Dr. Novick, applicants assert that it is clear that patients 15, 16 and 17 did not receive a course of therapy from three days to nine days, separated by a time of not receiving therapy and then receiving another course of therapy from three to nine days, as required the by pending claims.

Dr. Novick also points out that even with Patient 17 only receiving 2 days of treatment followed by another course of therapy (since Waters reports that patient 17 received a second course of therapy), Waters still does not teach or suggest the claimed method of treating cancer where the patient is given a course of therapy of three to nine days, followed by a rest period, followed by another three to nine day course of therapy. First, patient 17 only received a two-day dose of therapy as Waters states that treatment was discontinued after 48 hours. Dr. Novick further concludes that there is nothing to teach or suggest that Patient 17's second course of therapy was anything but the 14- day cycle of the planned treatment protocol. Therefore, there is nothing in Waters to teach or suggest the invention as claimed, let alone teach or suggest a second cycle consisting of three to nine days. See Declaration, paragraph 19.

Regarding Patient 18, Dr. Novick points out that the treatment was discontinued at day 8. However, he notes there is nothing in the article that states that Patient 18 went on to receive a second course of therapy. Waters mentions that only three patients (Patient 2, 17 and 21) received a second course of therapy. Waters does not teach or suggest that it was Patient 18 and in fact clearly indicates by deduction that it was not Patient 18. *See* page 1813, first col. and page 1818, first col. Thus, Dr. Novick concludes that there is no teaching or suggestion to shorten the course of therapy from 14 days to three to nine days and then continue on with another course of therapy of three to nine days after a rest period between. See Declaration, paragraph 20.

Thus, Dr. Novick concludes that there is nothing in Webb or Waters to teach or suggest a cycle of therapy to treat cancer consisting of three to nine days, followed by an interval of time where no bcl-2 antisense oligonucleotide is administered, followed by another three to nine day cycle of therapy (as required by the claims of the instant application). See Declaration, paragraph 22. He further states that in his opinion one skilled in the art with the knowledge of Webb and Waters would have <u>not</u> been motivated to treat cancer by shortening the cycle of therapy to from the accepted 2 week cycle of therapy to a cycle of therapy consisting of three to nine days, followed by an interval of time where no bcl-2 antisense oligonucleotide is administered, followed by another three to nine day cycle of therapy. See Declaration, paragraph 21-23.

Applicants therefore submit that the Examiner has taken the present claimed invention and read back into the Webb and Waters reference to find an alleged motivation. This is clearly hindsight, which is impermissible. Accordingly, applicants request withdrawal of this ground of rejection.

Claim rejections under 35 U.S.C. §103(a)

The Examiner has rejected claims 1 and 3-23 as unpatentable over Webb in view of Waters and Bennett. As discussed above, neither Webb nor Waters teach or suggest the claimed invention. Bennett does not cure these deficiencies. As such, applicants request withdrawal of this ground of rejection.

CONCLUSION

Applicants respectfully submit that, in view of the foregoing amendments and remarks, the present application is in condition for allowance. If the Examiner would like to discuss any remaining issues in this application, the Examiner is invited to contact the undersigned at the phone number provided below.

Applicants authorize the Commissioner to charge the requisite fee for the request for continuation examination as well as any other fee due or credit any overpayment arising from this communication to Deposit Account No. 11-0600.

Respectfully submitted,

Date: July 12, 2007

Joseph A. Coppola (Reg. No: 38,413)

KENYON & KENYON LLP
One Broadway
New York, NY 10004
(212) 425-7200 (Tel.)
(212) 425-5288 (fax)

OIPE
JUL 16 2007
PATENT & TRADEMARK OFFICE

Declaration of Dr. Steven Craig Novick

Qualifications of Dr. Novick

1. I, Dr. Steven Craig Novick, received a medical doctor degree from New York University School of Medicine in 1995. I received a doctorate degree in Molecular Oncology in 1994 from the same University. I have published numerous articles relating to various cancers and the use of certain therapies in the treatment of different cancers.

2. Since 2004, I have been serving as the Medical Director for Genta Incorporated. During this time I have assisted in the preparation of NDA filings for submission to the FDA to seek marketing approval for Genasense®. I assisted in the analysis and presentation of safety and efficacy data for Genasense. Genasense is a bcl-2 antisense oligonucleotide, also referred to as G3139.

Genasense Background and General Comments

3. Before the priority date of the '170 application (August 25, 2000), the generally accepted course of therapy was a 14-day treatment regimen. See chart attached at Tab A.

4. Not until after the present inventor's discovery that a shorter cycle of therapy would be useful in treating cancer, did others move to a shorter cycle of therapy. See chart at Tab B.

5. The first paper to discuss the use of a shorter treatment regimen (published after the filing date of the '170 application) was the Jansen et al. paper, Lancet, Vol. 356, pp. 17281733, (Nov. 18, 2000), which reports research sponsored by Genta. This paper shows efficacy in 14 patients where the patients received increased doses of BCL-2 antisense oligomer for a five-day cycle of therapy.

Summary of Conclusions: there is no teaching or suggestion in Webb and Waters to shorten the treatment regimen to less than a 2-week course of therapy

6. I have read and understood the subject application, U.S. 09/709,170 ("the '170 application").

7. I have also read the Office Action issued by the USPTO on November 28, 2006 and the two references referred to therein (Webb et al., The Lancet, 1997 Vol. 349; 1137-1141 ("Webb")) and Waters et al., Journal of Clinical Oncology, 2000 Vol. 18:1812-1823 ("Waters")).

8. I have concluded that one skilled in the art would not be motivated by the teachings of Webb and Waters to reduce the usual course of therapy for bcl-2 from a two week course of therapy to a three to nine day course of therapy, as presently claimed in the '170 patent.

9. The results reported in Webb and Waters are not impressive, and therefore, one skilled in the art reviewing these references would not be motivated to provide a shorter course of therapy, especially since most of all of the patients in the studies did not respond satisfactorily, despite 14 days of treatment. Those skilled in the art that develop drugs and treatment regimens do not routinely shorten cycles of therapy. To be motivated to do so (and to go against accepted treatment schedules) would require convincing results, which simply are not reported in Webb and Waters.

Webb Reference: no motivation to shorten the course of therapy

10. After reading the Webb reference, it is my opinion that this reference teaches a two-week treatment regimen. *See* Webb, p. 1137 left column: "A daily subcutaneous infusion of 18-base, fully phosphorothioated antisense oligonucleotide **was administered for 2 weeks** to nine patients. . . ." (emphasis added); *see also* page 1138, left column **"One 2-week course of treatment** was given. Patients were followed for 4 weeks after the end of treatment. If there was evidence of tumor response, a second course was considered." (emphasis added). Thus, in my opinion, one skilled in the art would read Webb as teaching a two-week course of therapy.

11. In my opinion, the mere fact that the authors in Webb report the bcl-2 levels of one patient (patient number 6) measured at week 1 and week 2 during the course of the two week course of treatment does not teach or suggest to one skilled in the art to treat a patient for cancer by shorting the regimen to less than the two week course of treatment, let alone shorten the course of treatment to a cycle of therapy consisting of three to nine days (as is presently claimed in the '170 application).

12. In my opinion, the mere fact that one patient (patient 6) at day 7 had reduced levels of BCL-2, does not provide evidence of treatment or a response, nor motivation to shorten the treatment regimen. One would not know whether the total infusion of 14 days was necessary to provide treatment of cancer or whether infusion of 7 days of therapy would be sufficient. This is especially the case, since the patient 6 did not show a promising cancer response.

13. One skilled in the art would understand that bcl-2 levels would in fact most likely go down with bcl-2 antisense treatment but would not know based on Webb's study whether this reduction represented a transient reduction or a stable reduction of bcl-2 levels. Further, one skilled in the art reading Webb would not know if this reduction of bcl-2 levels would likely treat cancer, especially if the bcl-2 reduction was transient.

14. In my opinion, one skilled in the art reading Webb would <u>not</u> be motivated to shorten the course of therapy, but rather would be motivated to continue with a longer course of therapy, or change the regimen to a course of therapy with a higher dose, or add to the regimen a second, third, or fourth (or more), course of therapy, or a combination of all of these changes to the regimen. In my opinion, by no means would one be motivated to shorten the course of therapy to treat cancer just because one patient showed reduced bcl-2 levels at week 1 and week 2, especially since patient 6 only showed a partial or negligible tumor response (page 2, column 1139).

15. Thus, it is my opinion that Webb does not teach or suggest changing the treatment regimen to anything shorter than a two-week course of therapy, let alone to a three to nine day course of therapy as presently claimed in the '170 application.

Waters reference: no motivation to shorten the course of therapy

16. After reviewing Waters, I conclude that this reference also teaches a course of therapy for two weeks. *See* Page 1812, first column: "Twenty-one patients with Bcl-2-positive relapsed NHL **received a 14-day subcutaneous infusion** of G3139. . ."(emphasis added); *see also* page 1813, left column: "Antisense oligonucleotide G3139 was delivered as a continuous subcutaneous infusion for **14 days** by a portable infusion pump. Toxicity was graded according to the common toxicity criteria and assessed **during the 2-week treatment period** and during the subsequent 4 weeks. One course of treatment was planned per patient, but additional courses of treatment were considered in the **event of a tumor response**." (emphasis added).

17. Because the purpose of this study was to determine safety ("These objectives provided the rationale for a phase I trial of antisense oligonucleotide G3139" page 1813, first col.), the authors studied and reported toxic events and noted that in certain patients, the treatment with bcl-2 antisense oligonucleotide was discontinued before completing the full 2-week course of therapy. See page 1815, col. 2. However, it is my opinion that stopping treatment during a course of therapy due to adverse events, does not teach or suggest using a shorter course of therapy to treat cancer.

18. Waters reports that certain patients had adverse effects and had their course of therapy terminated. For example, Patient 15's treatment was discontinued on day one, Patient 16's treatment was discontinued on day 12 and Patient 17's treatment was discontinued after day 2 (48 hours). *See* page 1815, col. 2. Thus, even if one skilled in the art would be motivated to shorten the cycle of therapy to treat cancer, there is nothing in this data to teach or suggest shortening the cycle of therapy to three to nine days, separated by an interval of time when the therapy is not given and repeating with another three to nine day cycle of therapy (as the current pending claim requires.)

19. Even if one were to read Waters as teaching Patient 17 only receiving 2 days of treatment followed by another course of therapy (since Waters reports that patient 17 received a second course of therapy), Waters still does not teach or suggest the claimed method of treating cancer where the patient is given a course of therapy of three to nine days, followed by a rest period, followed by another three to nine day course of therapy. First, patient 17 only received

two days of therapy as Waters states that treatment was discontinued after 48 hours because of dose limiting toxicity. Second, there is nothing to teach or suggest that Patient 17's second course of therapy at a lower dose was anything but the planned 14-day cycle required by the protocol. The discussion of Patient 17 therefore does not suggest the claimed invention, wherein multiple cycles of therapy each consist of three to nine days.

20. Waters reports that Patient 18's treatment was discontinued at day 8. However, there is nothing in article that states that Patient 18 went on to receive a second course of therapy. Waters mentions that only three patients (Patient 2, 17 and 21) received a second course of therapy. Waters but does not teach or suggest that it was Patient 18 and in fact clearly indicates by deduction that it was not Patient 18. *See* page 1813, first col. and page 1818, first col. Thus, there is no teaching or suggestion to shorten the course of therapy from 14 days to three to nine days and then continue on with another course of therapy of three to nine days after a rest period between.

21. In my opinion, even Waters was not impressed with the results of the study and therefore did not contemplate a shorter treatment regimen, but instead proposed a combination therapy. On page 1821, Waters notes that "[o]ne of the most interesting possibilities is their use as chemosensitizing agents . . . ." On page 1822, Waters further notes that "based on the results from this phase I study, a phase II trial is now in progress at Royal Marsden Hospital using G3139 in combination with standard cytotoxic regimens . . . " Thus, even Waters does not teach or suggest the use of a shorter treatment regimen, but rather suggest using BCL-2 in combination with cytotoxic reagents.

22. I, therefore, conclude that Waters does not teach or suggest a cycle of therapy to treat cancer consisting of three to nine days, followed by an interval of time where no bcl-2 antisense oligonucleotide is administered, followed by another three to nine day cycle of therapy (as required by the claims of the '170 application).

Conclusion

23. In addition to having no teaching or suggestion in Webb or Waters, it is my opinion, that one skilled in the art, reading Webb and Waters, would not have been motivated to treat cancer by shortening the cycle of therapy to from the accepted 2 week cycle of therapy to a cycle of therapy consisting of three to nine days, followed by an interval of time where no bcl-2 antisense oligonucleotide is administered, followed by another three to nine day cycle of therapy.

24. All statements made herein of my own knowledge are true, all statements made herein on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001, and may jeopardize the validity of the application or any patent issuing thereon.

4/25/07
Date

Dr. Steven Craig Novick

TAB A

Bcl-2 ANTISENSE PROTOCOLS ***BEFORE*** THE 09/709,170 APPLICATION PRIORITY DATE
April 26, 2006

AUTHOR	DATE	ROUTE	DAYS	COMMENTS
Webb	1997 ASCO (1997 Lancet)	SC Infusion (daily w/ portable syringe driver)	14	bcl-2 protein levels measured at start of treatment, 2 weeks and 6 weeks. One patient was apparently assayed at 7 days as well (#6, Fig. 2), and had stable disease at week 6 (pg. 1139, tumor response). Patient 2 also had a decrease in bcl-2 protein and stable disease. 8 of 9 patients had stable disease or progressive disease on the study (little or no therapeutic benefit). A correlation between bcl-2 reduction and tumor response is not disclosed or suggested.
Morris	1999 ASCO	IV Infusion	14	Patient bcl-2 levels not reported.
Waters	1999 ASCO	SC Infusion	14	bcl-2 protein levels measured in tumor samples of 13 patients, and after treatment was reduced in 5 patients. Contains no disclosure suggesting a correlation between bcl-2 reduction and tumor response.
Jansen	1999 ASCO	IV Infusion	14	Reduction in bcl-2 protein levels coincident with therapy. Contains no disclosure suggesting a correlation between bcl-2 reduction and tumor response.
Scher	2000 ASCO	Cont. Infusion	14-21	At 4.1 mg/kg/d, bcl-2 protein expression decreased within one week, peak effect at 8-15 days. Conclusion: G3139 can decrease bcl-2 protein expression. Contains no disclosure suggesting a correlation between bcl-2 reduction and tumor response.
Chen	2000 ASCO	Cont. Infusion	21	bcl-2 downregulation at doses $\geq$ 2 mg/kg/day. At 3 mg/kg/d, maximum bcl-2 reduction seen by day 3 of infusion. Tumor response observed in 2 patients. Contains no disclosure suggesting a correlation between bcl-2 reduction and tumor response.
Chi	2000 ASCO 2001 Clin Cancer Res	Cont. IV Infusion	14	bcl-2 expression evaluated, no disclosure of results in abstract. Journal disclosure: bcl-2 protein reduced in 5 of 5 patients at 5 mg/kg/d at day 8. Patient 23 had >50% reduction in PSA, described as a good therapeutic response, but had only 10% reduction in bcl-2 levels (Fig. 1 and Fig. 2). Compare Patients 20 & 24 with 25-50% reduction in bcl-2 (Fig. 2), but who are not listed among those having a tumor response.

Tab A

Waters	2000 J. Clin. Oncol. (May)	SC Infusion	14	See Tables 4 & 5. Patient 20's reduction in bcl-2 was less than half that of Patient 19 (15% vs. 36%) but both had stable disease. Patient 12 (32%) had a bcl-2 reduction comparable to Patient 19 (36%) but had progressive disease rather than stable disease. The largest bcl-2 reduction was Patient 6 (47%), who only had a minor response. Of the three patients who had bcl-2 analysis at day 7, Patient 11 and Patient 12 had dramatically different therapeutic outcomes (stable disease vs. progressive disease) despite comparable reductions in bcl-2 expression (24% and 36% respectively). 9 of 21 patients had no change in bcl-2 levels in any tissue analysed. Demonstrates there is no reliable correlation between reduction in bcl-2 expression and tumor response.

TAB B

BCL-2 ANTISENSE PROTOCOLS ***AFTER*** THE 09/709,170 APPLICATION PRIORITY DATE
April 26, 2006

AUTHOR	DATE	ROUTE	DAYS	COMMENTS
de Bono	2001 ASCO	Cont. IV Infusion	5	Marked downregulation of bcl-2 by day 5. Contains no disclosure suggesting a correlation between downregulation of bcl-2 and tumor response.
Ochoa	2001 ASCO	Cont. IV Infusion	1-8	Marked downregulation of bcl-2 by day 6 at 5 mg/kg/d. Contains no disclosure suggesting a correlation between downregulation of bcl-2 and tumor response.
Jansen	2001 ASCO	Cont. IV Infusion	5	bcl-2 downregulated by day 4. Contains no disclosure suggesting a correlation between downregulation of bcl-2 and tumor response.
Morris	2002 Clin. Cancer Res.	Cont. Infusion	14 or 21	bcl-2 protein levels are shown for a single patient, and did not decline until day 15 of treatment. **No major antitumor responses** were observed - 37% had stable disease during treatment and 57% progressed (pg. 681, col. 2, "Clinical Effects"). "These studies are ongoing, as are determination of the association between clinical effects, dose and the timing and degre of bcl-2 protein reduction." (pg. 682, last sentence)
Rudin	2003 ASCO 2004 J Clin Oncol	Cont. IV Infusion	1-8	**No evident suppression** of bcl-2 in peripheral blood mononuclear cells **on day 6** of treatment (pg. 1114, Analysis of bcl-2 Suppression..."). **These data are consistent with prior clinical reports** (pg. 1115, first column - see Waters - J Clin Onc 2000 and Morris - Clin Cancer Res 2002, above; Chi - Clin Cancer Res 2001 and Marcucci - Blood 2003, below).
Demidov	2003 ASCO	Cont. IV Infusion	7	Analysis of bcl-2 levels not disclosed.
Esteva	2004 ASCO	Cont. Infusion	5	Analysis of bcl-2 levels not disclosed.
Marshall	2004 Ann Oncol	Cont. Infusion	21 5	Dose limiting toxicities prevented dose escalation beyond 4 mg/kg/day in 21 day infusion protocol. In 5 day infusion protocol even highest doses were tolerated without dose limiting toxicity. **Shortened infusion had less cumulative toxicities and still allowed similar total delivery as the longer infusion.**

Tab B

BCL-2 ANTISENSE PROTOCOLS ***AFTER*** THE 09/709,170 APPLICATION PRIORITY DATE
April 26, 2006

Latest Priority Date of Genta Patent Application - 10 November 2000 - (Dark Line)
ASCO Annual Meetings are held in late May/early June

Conclusions: Prolonged infusion was the standard protocol prior to Nov. 2000.
Following filing of the Genta patent application, the field quickly adopted the short infusion protocol of the invention because it allowed higher doses to be tolerated.
Treatment of cancer does not necessarily result from decreases in bcl-2 levels .
Therefore, observation of bcl-2 downregulation does not indicate cancer is inherently treated.